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Brown, Sara J.

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Sara J. Brown

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JID | PERSPECTIVES | MONTAGNA SYMPOSIUM

What have we learned from GWAS for atopic dermatitis?

Sara J Brown¹¹Skin Research Group, Division of Molecular and Clinical Medicine, School of Medicine, University of Dundee, Scotland, UKs.j.brown@dundee.ac.uk

ORCID: 0000-0002-3232-5251

@drsarabrown

Abstract

Genome-wide association studies (GWAS) have revealed multiple loci associated with atopic dermatitis (AD). Some have confirmed pre-existing knowledge, including the role of skin barrier and type 2 inflammation in AD pathogenesis, whilst others have provided newer insights, including evidence of auto-immunity and previously unrecognized genes controlling epidermal differentiation. The majority of risk loci are in intergenic regions for which functional mechanism(s) remain unknown; these loci require detailed molecular studies, carried out in cells and tissues of relevance to AD. Genomic findings to date account for ~30% of AD heritability, so considerable further work is needed to fully understand individual risk.

An introduction to GWAS

A genome-wide association study (GWAS) aims to identify regions of the genome that are associated with a specific trait or disease (<https://ghr.nlm.nih.gov/primer/genomicresearch/gwastudies>). The technique compares the frequency of single nucleotide polymorphisms (SNPs) and other types of variants (*eg* deletions and insertions) between cases and controls, similar to a massive case-control study. Large numbers variants are assessed (one-two million may be screened directly and many more by imputation), sampling regions across the whole genome and large numbers (thousands - tens of thousands) of cases and controls are needed to achieve sufficient statistical power. Results may be summarized in the form of a Manhattan plot (**Figure 1**). Complex traits result from the interactions of multiple genetic effects, many of which have small effect sizes. GWAS is a feasible approach for the study of common complex traits, because a sufficient sample size can be obtained. The effect sizes detected by GWAS can range from odds ratio (OR) >2 (*ie* risk more than doubled) to very small effect sizes (OR 1.1 or lower *ie* <10% increased risk).

GWAS applied to atopic dermatitis

Atopic dermatitis (AD) is common (affecting 0.2 to 24.6% of children (Brown et al., 2008, Odhiambo et al., 2009), up to 10% of adults (Bieber, 2008)) and a complex trait, caused by the interactions of multiple genetic and multiple environmental factors. AD is highly heritable (72–86 % concordance in monozygotic twin pairs (Larsen et al., 1986, Schultz Larsen, 1993)) and this provides the rationale for genetic studies. GWAS and GWAS meta-analysis have revealed ~31 loci associated with AD including four with secondary independent signals (Paternoster et al., 2015). Some AD risk loci have confirmed pre-existing knowledge, including the role of skin barrier and type 2 inflammation in AD pathogenesis: the epidermal differentiation complex on chromosome 1q21.3 includes *FLG*, encoding filaggrin and

the cytokine cluster on chr5q31.1 includes genes encoding IL-13 and IL-4 (**Figure 1**). Other loci have provided newer insights, including evidence for auto-immunity (Paternoster et al., 2015) and a role for Langerhans cells, indicated by variants in a locus on 2p13.3 which affect the expression levels of CD207/langerin in skin (Paternoster et al., 2015).

GWAS of multiple atopic traits has shown considerable overlap in genetic risk profiles for AD, asthma and allergic rhinitis (Ferreira et al., 2017, Ferreira et al., 2019) attributed predominantly to lymphocyte-mediated immunity. Only two loci indicate AD-specific effects and these are both within the epidermal differentiation complex on chromosome 1q21.3, attributed to *FLG* and *HRNR-RPTN* (Ferreira et al., 2017).

An extension to GWAS, focusing on protein-coding variants, used exome genotype and skin transcriptome data (Mucha et al., 2019). This study identified an additional 12% of AD heritability explained by rare protein-coding variation in genes including *IL4R*, *IL13*, *JAK1*, *JAK2* and *TYK2*, as well as novel candidate genes *DOK2* and *CD200R1*.

Outstanding questions

The most highly significant peak, on chromosome 1q21.3, includes the well-known *FLG* AD risk (Irvine et al., 2011) but loss-of-function mutations and copy number variation within *FLG* (Brown et al., 2012) do not fully explain this strong effect. It is therefore likely that the epidermal differentiation complex, a dense cluster of 63 genes (de Guzman Strong et al., 2010) contains additional risk mechanisms (Paternoster et al., 2011, Paternoster et al., 2015). Variants in *FLG2* may contribute to AD persistence (Margolis et al., 2014) and an in-frame deletion in *SPRR3* has been associated with AD (Marenholz et al., 2011), but additional genetic and epigenetic mechanisms in this highly repetitive and therefore challenging region remain to be defined.

The majority of loci identified by GWAS are in intergenic regions for which functional mechanism(s) remain unknown; these loci require detailed molecular studies, carried out in cells and tissues of relevance to AD. One locus for which functional studies have been conducted is on chromosome 11q13.5 (Esparza-Gordillo et al., 2009, O'Regan et al., 2010). The risk SNPs lie in a long intergenic region between *EMSY* and *LRRC32*; both are strong candidate genes for AD risk. *EMSY* encodes a transcriptional regulator previously uncharacterized in skin. We have shown that *EMSY* acts as a transcriptional repressor in keratinocytes, controlling multiple aspects of skin barrier formation (Elias et al., 2019). *LRRC32* encodes a transmembrane receptor on activated T-regulatory cells that modulates TGF-beta activity; there is evidence of a functional variant in *LRRC32* which may play a role in AD (Manz et al., 2016). Both skin and blood are likely to be tissues with direct relevance to the pathophysiology of AD. Differential methylation has shown that skin tissue shows greater epigenetic dysregulation than blood from AD patients (Rodriguez et al., 2014) but the specific cell types implicated in GWAS risk mechanisms remains an question of importance.

GWAS findings to date account for <20% of AD heritability (Paternoster et al., 2015) and even with the additional risk attributed to protein-coding variants, ~70% of heritability remains to be explained (Mucha et al., 2019). Considerable further work is therefore needed to fully understand individual risk.

Complimentary approaches

Other approaches have used GWAS data to leverage additional understanding of the molecular mechanisms underpinning AD. A genome-wide comparative analysis of AD versus psoriasis showed

that opposing mechanisms appear to be more prominent than shared effects for these patterns of skin inflammation (Baurecht et al., 2015). Opposing loci include the Th2 locus control region (chromosome 5q31.1), epidermal differentiation complex (overlying a long non-coding RNA, *FLG-AS1*) and the major histocompatibility complex (chromosome 6p21-22). Previously unreported pleiotropic alleles with opposing effects on atopic dermatitis and psoriasis risk were identified in *PRKRA* and *ANXA6/TNIP1*.

Mendelian randomization (MR) is a statistical analysis technique that uses genetic risk to define phenotypes; this circumvents some of the limitations in conventional epidemiology, including confounding and reverse causation (Budu-Aggrey and Paternoster, 2019). SNPs from GWAS are used in MR as a proxy for AD and other phenotypes and this approach can be used to distinguish causation from association. MR studies in AD have investigated causal links with prenatal alcohol exposure (Shaheen et al., 2014) and vitamin D levels (Manousaki et al., 2017), each have no causal effect on AD. Another approach has combined MR and multiple-trait colocalization to define cell-specific inflammatory drivers of autoimmune and atopic disease (McGowan et al., 2019).

Longitudinal latent class analysis uses phenotypic data at multiple timepoints to define subgroups within the heterogeneous patient population by mathematical modelling. Large population cohort studies from the UK and Netherlands showed five distinct subgroups of AD with remarkable replication (Paternoster et al., 2018). GWAS SNPs mapped to these subgroups revealed the strongest association with most persistent disease. However, further work is required to gain a sufficiently powerful genetic risk score to prospectively predict an individual's trajectory for AD.

Future perspectives

Findings from multiple GWAS studies have re-emphasized the importance of genetic risk mechanisms controlling both the skin barrier and immune responses in AD. But important questions remain (**Figure 2**). The threshold for statistical significance is necessarily stringent in GWAS because of the extreme multiple testing that occurs (**Figure 1**). Larger GWAS studies, including hundreds of thousands of cases and controls could reveal additional risk loci, but each new effect size is likely to be small. Gene-gene interaction analysis is also statistically challenging because of the issues of multiple testing and similarly gene-environment interactions, whilst likely to be of importance in AD, are challenging to detect on a genome-wide level. These mechanisms therefore require alternative, more targeted functional assessment (**Figure 2**).

The majority of GWAS performed to date have used white European and selected Asian populations. The lack of ethnic diversity in genetic research has been highlighted as a critical weakness in the field, not least in terms of equity in access to medical and scientific knowledge but also as a missed opportunity for genetic discovery (Hindorff et al., 2018). The GWAS meta-analysis performed in 2015 was a 'multi-ancestry' study (Paternoster et al., 2015) but only ~2% of cases and <1% of controls were of African-American ancestry. AD GWAS studies in more diverse ethnicities, including African populations, are ongoing.

It is known that drugs targeting molecules or pathways informed by human genetic studies have above-average chance of clinical success (Kamb et al., 2013). The genome-wide approach (described above) to define variants in protein-coding regions identified multiple proteins in the IL-13 pathway, and all have been successfully targeted in novel AD treatments (Mucha et al., 2019). Translational genomics, drug development and personalised medicine will progress in tandem (**Figure 2**) (Dugger et

al., 2018, Zeggini et al., 2019) and dermatological research is poised to be at the forefront of these exciting developments in clinical care.

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Figure titles and legends

Figure 1. Summary of key features in a Manhattan plot

A Manhattan plot is the conventional method for displaying results from GWAS. Each SNP is represented by a dot on the plot, and its position is determined by genomic location and a statistical test of association with the trait of interest.

Figure 2. Future work needed to build on GWAS for the benefit of patients with AD

Additional GWAS are likely to increase understanding but extensive follow-up work is required to test and validate functional effects at a molecular level before progress can be made in personalized medicine and rational drug design.

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